

Claims

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1. A method for arresting, protecting and/or preserving an organ which includes administering effective amounts of (i) a potassium channel opener or agonist and/or an adenosine receptor agonist and (ii) local anaesthetic to a subject in need thereof.

2. A method as claimed in claim 1, wherein the organ is either intact in the body of the subject or isolated.

3. A method as claimed in claim 1 or 2, wherein the organ is a circulatory organ, respiratory organ, urinary organ, digestive organ, reproductive organ, neurological organ or somatic cell.

4. A method as claimed in claim 3, wherein the circulatory organ is a heart.

5. A method as claimed in claim 4, which is used to arrest, protect and/or preserve the heart during open-heart surgery, reduce heart damage before, during or following cardiovascular intervention or protect those portions of the heart that have been starved of normal flow, nutrients and/or oxygen.

6. A method as claimed in any one of claims 1 to 5, wherein the potassium channel opener or agonist is selected from nicorandil, diazoxide, minoxidil, pinicadil, aprikalim, cromokulim, NS-1619 (1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]5-(trifluoromethyl)2-H-benimidazol-one), amlodipine, Bay K 8644(L-type)(1,4-dihydro-26-dimethyl-5-nitro-4[2(trifluoromethyl)phenyl]-3-pyridine carboxylic acid (methyl ester)), bepridil HCl (L-type), calciseptine (L-type), omega-conotoxin GVIA (N-type), omega-conotoxin MVIIIC (Q-type), cyproheptadine HCl, dantrolene sodium (Ca^{2+} release inhibitor), diltiazem HCl (L-type), filodipine, flunarizine HCl ($\text{Ca}^{2+}/\text{Na}^+$), fluspirilene (L-type), HA-1077 2HCl(1-(5 isoquinolinyl sulphonyl) homo piperazine.HCl), isradipine, loperamide HCl, manoalide (Ca^{2+} release inhibitor), nicardipine HCl (L-type), nifedipine (L-type), nifuglidipine HCl (L-type), nimodipine (L-type), nitrendipine (L-type), pimozone (L- and T- type), ruthenium red, ryanodine (SR channels), taicatoxin, verapamil HCl (L-type), methoxy-verapamil HCl (L-type), YS-035 HCl (L-type)N[2(3,4-

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(dimethoxyphenyl)ethyl]-3,4-dimethoxy N-methyl benzene ethaneamine HCl) and AV blockers.

7. A method as claimed in claim 6, wherein the AV blocker is adenosine.
8. A method as claimed in any one of claims 1 to 7, wherein the adenosine receptor agonist is selected from N⁶-cyclopentyladenosine (CPA), N-ethylcarboxamido adenosine (NECA), 2-[p-(2-carboxyethyl)phenethyl-amino-5'-N-ethylcarboxamido adenosine (CGS-21680), 2-chloroadenosine, N⁶-[2-(3,5-dimethoxyphenyl)-2-(2-methoxyphenyl)]ethyladenosine, 2-chloro-N⁶-cyclopentyladenosine (CCPA), N-(4-aminobenzyl)-9-[5-(methylcarbonyl)-beta-D-robifuranosyl]-adenine (AB-MECA), ([IS-[1a,2b,3b,4a(S*)]]-4-[7-[[2-(3-chloro-2-thienyl)-1-methyl-propyl]amino]-3H-imidazole[4,5-b]pyridyl-3-yl]cyclopentane carboxamide (AMP579), N⁶-(R)-phenylisopropyladenosine (R-PLA), aminophenylethyladenosine 9APNEA) and cyclohexyladenosine (CHA).
9. A method as claimed in any one of claims 1 to 8, wherein the local anaesthetic is selected from mexiletine, diphenylhydantoin, prilocaine, procaine, mepivacaine and Class 1B antiarrhythmic agents.
10. A method as claimed in claim 9, wherein the class 1B antiarrhythmic agent is lignocaine.
11. A method as claimed in any one of claims 1 to 10, wherein active ingredients (i) and (ii) are administered together with a pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient.
12. A method as claimed in claim 11, wherein the pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient is a buffer having a pH of about 6 to about 9.
13. A method as claimed in claim 11 or 12, wherein the pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient has low concentrations of potassium.
14. A method as claimed in claim 13, wherein the concentration of potassium is up to about 10mM.

15. A method as claimed in any one of claims 12 to 14, wherein the buffer is Krebs-Henseleit, St. Thomas No. 2 solution, Tyrodes solution, Femes solution, Hartmanns solution or Ringers-Lactate.

16. A method as claimed in any one of claims 11 to 15, wherein the 5 pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient has low concentrations of magnesium.

17. A method as claimed in claim 16, wherein the concentration of magnesium is up to about 2.5mM.

18. A method as claimed in any one of claims 1 to 17, wherein the active 10 ingredients (i) and (ii) are administered together with another medicament.

19. A method as claimed in claim 18, wherein the medicament is dipyridamole or a clot-busting drug.

20. A method as claimed in claim 19, wherein the clot-busting drug is streptokinase.

15 21. A method as claimed in any one of claims 1 to 20, wherein the subject is a neonate/infant.

22. A method as claimed in any one of claims 4 to 21, wherein the administration in cardiovascular applications is achieved by mixing the active 20 ingredients with the blood of the subject and/or a subject having a similar blood type.

23. A method as claimed in any one of claims 1 to 22, wherein arrest is achieved by either continuous or intermittent delivery.

24. A method as claimed in any one of claims 1 to 23, wherein the arrest occurs at temperatures of about 15°C to about 37°C.

25. Use of (i) a potassium channel opener or agonist and/or an adenosine receptor agonist and (ii) a local anaesthetic in the manufacture of a medicament 25 for arresting, protecting and/or preserving an organ.

26. A (i) potassium channel opener or agonist and/or an adenosine receptor agonist and (ii) a local anaesthetic for use in arresting, protecting and/or 30 preserving an organ.

27. A method for arresting, protecting and/or preserving an organ which comprises adding a composition which includes effective amounts of (i) a potassium channel opener or agonist and/or an adenosine receptor agonist and (ii) a local anaesthetic to the organ.

5 28. A pharmaceutical or veterinary composition which includes effective amounts of (i) a potassium channel opener or agonist and/or an adenosine receptor agonist and (ii) a local anaesthetic.

29. A composition as claimed in claim 28, wherein the potassium channel opener or agonist is selected from nicorandil, diazoxide, minoxidil, pinicadil,
10 aprikalim, cromokulim, NS-1619 (1,3-dihydro-1-[2-hydroxy5(trifluoromethyl)phenyl]5-(trifluoromethyl)2-H-benimidazol-one), amlodipine, Bay K 8644(L-type)(1,4-dihydro-26-dimethyl-5-nitro-4[2(trifluoromethyl)phenyl]-3-pyridine carboxylic acid (methyl ester)), bepridil HCl (L-type), calciseptine (L-type), omega-conotoxin GVIA (N-type), omega-conotoxin MVIIIC (Q-type), cyproheptadine HCl, dantrolene sodium (Ca^{2+} release inhibitor), diltiazem HCl (L-type), filodipine, flunarizine HCl ($\text{Ca}^{2+}/\text{Na}^+$), fluspirilene (L-type), HA-1077 2HCl(1-(5 isoquinolinyl sulphonyl) homo piperazine.HCl), isradipine, loperamide HCl, manoalide (Ca^{2+} release inhibitor), nicardipine HCl (L-type), nifedipine (L-type), niguldipine HCl (L-type), nimodipine (L-type), nitrendipine (L-type), pimozone (L- and T- type), ruthenium red, ryanodine (SR channels), taicatoxin, verapamil HCl (L-type), methoxy-verapamil HCl (L-type), YS-035 HCl (L-type)N[2(3,4-dimethoxyphenyl)ethyl]-3,4-dimethoxy N-methyl benzene ethaneamine HCl) and AV blockers.

20 25 30. A composition as claimed in claim 29, wherein the AV blocker is adenosine.

31. A composition as claimed in claims 28 to 30, wherein the adenosine receptor agonist is selected from N^6 -cyclopentyladenosine (CPA), N -ethylcarboxamido adenosine (NECA), 2-[p-(2-carboxyethyl)phenethyl-amino-
30 5'-N-ethylcarboxamido adenosine (CGS-21680), 2-chloroadenosine, N^6 -[2-(3,5-dimethoxyphenyl)-2-(2-methoxyphenyl)ethyladenosine, 2-chloro- N^6 -

cyclopentyladenosine (CCPA), N-(4-aminobenzyl)-9-[5-(methylcarbonyl)-beta-D-robofuranosyl]-adenine (AB-MECA), ([IS-[1a,2b,3b,4a(S*)]]-4-[7-[[2-(3-chloro-2-furyl)-1-methyl-propyl]amino]-3H-imidazole[4,5-b]pyridyl-3-yl]cyclopentane carboxamide (AMP579), N⁶-(R)-phenylisopropyladenosine (R-PLA), aminophenylethyladenosine 9APNEA) and cyclohexyladenosine (CHA).

32. A composition as claimed in claims 28 to 31, wherein the local anaesthetic is selected from mexiletine, diphenylhydantoin, prilocaine, procaine, mepivacaine and Class 1B antiarrhythmic agents.

33. A composition as claimed in any one of claims 28 to 32 wherein the composition is a cardioplegic or cardioprotectant composition.

34. A composition as claimed in any one of claims 28 to 33, wherein active ingredients (i) and (ii) are administered together with a pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient.

35. A composition as claimed in claim 34, wherein the pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient, is a buffer having a pH of about 6 to about 9.

36. A composition as claimed in claim 34 or 35, wherein the pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient has low concentrations of potassium.

37. A composition as claimed in claim 36, wherein the concentration of potassium is up to about 10mM.

38. A composition as claimed in any one of claims 35 to 37, wherein the buffer is Krebs-Henseleit, St. Thomas No. 2 solution, Tyrodes solution, Femes solution, Hartmanns solution or Ringers-Lactate.

39. A composition as claimed in any one of claims 34 to 38, wherein the pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient has low concentrations of magnesium.

40. A composition as claimed in claim 39, wherein the concentration of magnesium is up to about 2.5mM.

41. A composition as claimed in any one of claims 29 to 40, wherein the active ingredients (i) and (ii) are administered together with another medicament.

42. A composition as claimed in claim 41, wherein the medicament is 5 dipyridamole or a clot-busting drug.

43 A composition as claimed in claim 42, wherein the clot-busting drug is streptokinase.

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